REMARKS

Claims 1-5, 7-10, 15, and 28 were examined. In the office action, the Examiner objected to claims 5 and 8-10 and rejected claims 1-5, 7-15 and 28. Applicants have canceled claims 3, 7, 9-14, and 16-27. Claims 1, 2, 4, 5, 8, 15, and 28 have been amended herein. New claims 29-35 have been added. Thus claims 1, 2, 4, 5, 8, 15, and 28-35 are pending.

Amended claim 1 relates to a method that involves quantitating the amount of bioactive IL-1β based on the amount of IL-6 produced by stromal cells cultured with a bone marrow preparation from an individual diagnosed with a multiple myeloma-related plasmaproliferative disorder. Support for this amendment can be found in original claim 2 and in the specification at, for example, page 4, lines 11-12, and page 10, line 26 through page 11, line 2. Amended claim 2 recites that the multiple myeloma-related plasmaproliferative disorder is smoldering multiple myeloma, and amended claim 28 recites that the multiple myeloma-related plasmaproliferative disorder is indolent multiple myeloma. Support for these claims can be found in the specification at page 7, lines 17-18, for example.

Claim 4 has been amended to refer to a method for quantitating IL-6. The method involves providing bone marrow preparations from an individual diagnosed with a multiple myeloma-related plasmaproliferative disorder and from a normal individual, and determining the amount of IL-6 produced by stromal cells cultured with these bone marrow preparations. The relative amounts of IL-6 can indicate whether the individual with a multiple myeloma-related plasmaproliferative disorder is likely to progress to active MM. Support for this amendment can be found in original claim 4 and in the specification at page 8, line 15 through page 9, line 10, and page 11, lines 24-25, for example.

Claims 5 and 8 have been amended to correct their dependency.

Claim 15 has been amended to recite that a measured amount of IL-6 in an individual undergoing treatment for MM is compared to a prior amount of IL-6 from the same individual, and that an increase relative to the prior amount is indicative of progression of MM, a decrease in the amount is indicative of regression of MM, and little or no change in the amount of IL-6 is indicative that the MM is stable. Support for this amendment can be found in the specification

at, for example, page 5, lines 1-5, page 9, lines 7-10, and page 10, lines 2-12. No new matter has been added by these amendments.

Applicants have added claims 29 through 32 herein. Claim 29 recites that the multiple myeloma-related plasmaproliferative disorder of claim 1 is monoclonal gammopathy of undetermined significance (MGUS). Claims 30 and 31 recite that the multiple myeloma-related plasmaproliferative disorder of claim 4 is indolent multiple myeloma or MGUS, respectively. Support for these new claims can be found in the specification at page 7, lines 17-18, for example. Claim 32 relates to a method for monitoring the status of MM in an individual by measuring the amount of IL-6 produced by stromal cells cultured with a bone marrow preparation from the individual, and comparing the measured amount of IL-6 with the amount of IL-6 produced by stromal cells cultured with a standard concentration of recombinant IL-1β. According to claim 32, progression of MM is indicated if the amount of IL-6 is higher than the amount of IL-6 produced by stromal cells cultured with a standard concentration of recombinant IL-1β, improvement of MM is indicated if the measured amount of IL-6 is lower than the amount of IL-6 produced by stromal cells cultured with a standard concentration of recombinant IL-1β, and the MM is considered to be stable if the amount of IL-6 is similar to the amount of IL-6 produced by stromal cells cultured with a standard concentration of recombinant IL-1β. Claims 33, 34, and 35 recite that the multiple myeloma-related plasmaproliferative disorder of claim 32 is smoldering multiple myeloma, indolent multiple myeloma, or MGUS, respectively. Support for new claim 32 can be found in original claim 15, and in the specification at page 11, lines 24-28, for example. Support for new claims 33-35 can be found at page 7, lines 17-18, for example. No new matter has been added by these new claims.

Applicants have canceled claims 11-14 and 16-27. The restriction requirement, however, remains traversed on the grounds previously presented and the Examiner is respectfully requested to reinstate these claims.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1, 2, 4, 5, 8, 15, and 28-35.

Objections

The Examiner objected to claims 5, 8 and 10 under 37 C.F.R. § 175(c) as being of improper dependent form. The Examiner also objected to claims 8, 9 and 10 under 37 C.F.R. § 175(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. Applicants have canceled claims 9 and 10, and have amended claims 5 and 8 to correct claim dependency. Applicants respectfully request withdrawal of the objection to claims 5 and 8 under 37 C.F.R. § 1.75(c).

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Carter (1990 British Journal of Haematology 74:424-431). The Examiner asserted that Carter teaches a dose dependent correlation between IL-1β and IL-6, and that culturing myeloma cells with stromal cells led to IL-6 production, which could be blocked by anti IL-1β antibodies.

Applicants respectfully traverse with respect to amended claims 1 and 2. Claim 1 has been amended to recite that IL-1β is quantitated in a bone marrow preparation from an individual diagnosed with a multiple myeloma-related plasmaproliferative disorder. Claim 2 has been amended to recite that the multiple myeloma-related plasmaproliferative disorder is smoldering multiple myeloma. Carter does not use myeloma cells from such individuals, and therefore does not anticipate claim 1 or claim 2 as amended. The Examiner is requested to withdraw the rejection of claims 1 and 2 under 35 U.S.C. § 102(b).

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1-5, 7, 15 and 28 under 35 U.S.C. § 103(a) as being unpatentable over Carter (*supra*) and Klein (1989 Blood 73(2):517-526). The Examiner asserted that while Carter does not teach the correlation of IL-6 to disease state, Klein teaches that bone marrow from patients with inactive/slightly active myeloma could be distinguished from bone marrow from patients with fulminating disease on the basis of IL-6 levels. The Examiner further asserted that it would have been obvious "to measure the level of IL-6 in a myeloma cell-stromal cell co-culture of Carter to determine the status of an individual or monitor the status of an individual as shown by Klein."

While the Examiner is correct in stating that Carter does not teach the correlation of IL-6 to disease state, Applicants respectfully submit that it would not have been obvious to combine Carter and Klein to achieve the instantly claimed methods.

Proper analysis under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process, and (2) whether the prior art also would have suggested that in so carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 288, 20 USPQ2d 1438 (Fed. Cir. 1991). Furthermore, the prior art must be considered as a whole.

> In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention. Evidence that supports, rather than negates, patentability must be fairly considered.

In re Dow Chemical Co. 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

A number of references in the prior art taught that IL-1β is not present in myeloma cells and that IL-1β is not correlated with disease state. Copies of the references referred to below are attached with the enclosed Information Disclosure Statement. For example, Sati et al. (*Br. J. Haematol.* 104:350-357, 1999) discloses that myeloma cells themselves do not produce the IL-1β protein. See, e.g., the abstract on page 350, and the left column on page 356. Borset et al. (*Br. J. Haematol.* 85:446-451, 1993) teaches that myeloma cells are not responsible for the overproduction of either IL-6 or IL-1. See, e.g., the abstract on page 446, and the third full paragraph on page 449. Furthermore, Kiss et al. (*Leuk. Lymphoma* 14:335-340, 1994) failed to observe a correlation between IL-6, IL-1β, and myeloma disease state. See, e.g., the abstract and the first paragraph on page 335, paragraph 2 on page 337, paragraph 1 on page 338, and paragraph 2 on page 339.

Klein evaluated the amount of IL-6 in MM patients. See, Klein at page 519. In contrast, the Applicants disclose methods for determining the amount of IL-1β in IMM, SMM, or MGUS patients (or the amount of IL-6 produced in response to IL-1β made by bone marrow preparations from such patients). In fact, Klein teaches away from correlating IL-1β with IMM,

SMM, or MGUS disease state. The final sentence on page 519 states, "Thus, neither LAF, IL-1β, nor TNF activity significantly discriminated between any categories of bone marrow, as opposed to IL-6." This statement shows that Klein did not consider IL-1β relevant to MM, and implies that it would not be relevant to IMM, SMM, or MGUS. In view of the above, the method of quantitating IL-1β as recited in claim 1 is patentably nonobvious. Methods of quantitating IL-6 as recited in claims 4 and 15 also are patentably nonobvious. Thus, the instant claims are not obvious over Carter in view of Klein, and withdrawal of the rejection of claims 1, 2, 4, 5, 15, and 28 under 35 U.S.C. § 103(a) is proper.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1, 3, 4, and 15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserted that the basis of the correlation between IL-1β and IL-6 in claim 1 is not clear, and that the conclusion of the method also is not clear. The Examiner also stated that the term "elevated" is a relative term that renders claims 3 and 4 indefinite, and that the specification does not provide a standard for determining the requisite degree of elevation. The Examiner also stated that it is not clear what level is to give a likelihood that correlates with "indicative of" or "likely to progress" to disease state. With regard to claims 3, 4, and 7, the Examiner inquired about the metes and bounds of the certainty of diagnosis or determining the likelihood of progression to disease, and asked whether there are false positives or false negatives.

With respect to claim 1, Applicants submit that a statement as to the basis of the correlation between IL-1β and IL-6 is not required. As stated in *Newman v. Quigg*, 877 F.2d 1575, 11 USPQ2d 1340 (Fed. Cir. 1989), "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." Applicants have amended claim 1 herein to recite that the conclusion of the method involves quantitating the amount of IL-1β based on its positive correlation to the amount of IL-6.

Applicants have canceled claims 3 and 7, thus obviating the Examiner's rejection. Amended claim 4 does not contain the term "elevated level," but rather relates to whether the amount of IL-6 produced by stromal cells cultured with a bone marrow preparation from an

individual diagnosed with a multiple myeloma-related plasmaproliferative disorder is greater or less than the amount of IL-6 produced by stromal cells cultured with a bone marrow preparation from a normal individual. The metes and bounds of the certainty of diagnosis are obviated by this amendment.

Finally, the Examiner asserted that in claim 15 the "known standard or a patient determined standard" is not clear, and stated that the method is not complete because there is no conclusion. Claim 15 has been amended herein to recite that the measured amount of IL-6 is compared to a prior amount of IL-6 measured in a bone marrow preparation from the same individual. Amended claim 15 also recites how the IL-6 amounts relate to the status of the individual. As stated above, it is not necessary for the inventors to know or for the claim to recite what causes the change in status.

In light of these amendments and remarks, Applicants respectfully request withdrawal of the rejection of claims 1, 4, and 15 under 35 U.S.C. § 112, second paragraph.

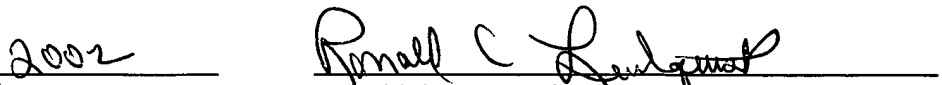
CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment.

Applicants ask that claims 1, 2, 4, 5, 8, 15, and 28-35 be allowed. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: Sept 17, 2002



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Version with markings to show changes made

In the claims:

Claims 3, 7, 9-14, and 16-27 have been cancelled.

Claims 1, 2, 4, 5, 8, 15, and 28 have been amended as follows:

1. (**Amended**) A method of quantitating bioactive IL-1β [in a bone marrow preparation], said method comprising:

a) determining the amount of IL-6 produced by stromal cells cultured with [said] a bone marrow preparation from an individual diagnosed with a multiple myeloma-related plasmaproliferative disorder; and

b) [correlating] quantitating the amount of bioactive IL-1β in said bone marrow preparation based on the amount of IL-6 produced by said stromal cells [to the amount of IL-1β in said bone marrow preparation].

2. (**Amended**) The method of claim 1, wherein said bone marrow preparation is from an individual diagnosed with smoldering multiple myeloma.

4. (**Amended**) A method of [determining likelihood of progression to active multiple myeloma in an individual] quantitating IL-6, said method comprising:

(a) [determining the amount of IL-6 produced by stromal cells cultured with] providing a first bone marrow preparation from an individual[, wherein an elevated level of IL-6 indicates said individual is likely to progress to active multiple myeloma] diagnosed with a multiple myeloma-related plasmaproliferative disorder and a second bone marrow preparation from a normal individual; and

(b) quantitating the amount of IL-6 produced by stromal cells cultured with said first and second bone marrow preparations, wherein progression to multiple myeloma is indicated if said amount of IL-6 produced by stromal cells cultured with said first bone marrow preparation is greater than said amount of IL-6 produced by stromal cells cultured with said second bone

marrow preparation, and wherein progression to multiple myeloma is not indicated if said amount of IL-6 produced by stromal cells cultured with said first bone marrow preparation is less than or similar to said amount of IL-6 produced by stromal cells cultured with said second bone marrow preparation.

5. (**Amended**) The method of claim [5] 4, wherein said [individual has been diagnosed with a] multiple myeloma-related plasmaproliferative disorder is smoldering multiple myeloma.

8. (**Amended**) The method of any one of claims [1-8] 1, 2, 4, or 5, wherein said bone marrow preparation is selected from the group consisting of a fresh supernatant from cultured bone marrow cells, a previously frozen supernatant from cultured bone marrow cells and a mononuclear cell preparation purified from bone marrow.

15. (**Amended**) A method of monitoring the status of multiple myeloma in an individual, said method comprising:

a) [determining the amount of IL-6 produced by stromal cells cultured with a] obtaining an earlier bone marrow preparation and a later bone marrow preparation from said individual, said individual [diagnosed with and] undergoing treatment for multiple myeloma, at least one of said bone marrow [preparation] preparations obtained after initiation of said treatment; and

b) [comparing said amount of IL-6 with a known standard or a patient determined standard] determining the amount of IL-6 produced by stromal cells cultured with said earlier bone marrow preparation and determining the amount of IL-6 produced by stromal cells cultured with said later bone marrow preparation, wherein progression of said multiple myeloma status is indicated if said amount of IL-6 produced by stromal cells cultured with said later bone marrow preparation is greater than said amount of IL-6 produced by stromal cells cultured with said earlier bone marrow preparation, wherein improvement of said multiple myeloma status is indicated if said amount of IL-6 produced by stromal cells cultured with said later bone marrow preparation is less than said amount of IL-6 produced by stromal cells cultured with said earlier bone marrow preparation, and wherein stability of said multiple myeloma status is indicated if

said amount of IL-6 produced by stromal cells cultured with said later bone marrow preparation is similar to said amount of IL-6 produced by stromal cells cultured with said earlier bone marrow preparation.

28. **(Amended)** The method of claim 1, wherein said bone marrow preparation is from an individual diagnosed with [a multiple myeloma-related plasmaproliferative disorder] indolent multiple myeloma.